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Familial association of abstinent remission from alcohol use disorder in first-degree relatives of alcohol-dependent treatment-seeking probands

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ABSTRACT

Background and Aims Studies that have included family history of alcohol use disorder (AUD) as a predictor of remission from AUD have yielded few significant results. The goals of this study were to estimate the association of persistent AUD, non-abstinent remission and abstinent remission ('AUD/remission status') in a proband with AUD/remission status in a relative and to test whether this association differed in related and unrelated proband-relative pairs. **Design** High-risk family study of alcohol dependence. Probands were recruited from treatment settings and relatives were invited to participate. Baseline assessments occurred between 1991 and 1998 with follow-up between 1996 and 2005. Half of probands were matched with a biological 1st-degree relative with life-time AUD (related group) and half of probands were paired with an unrelated individual with life-time AUD (unrelated group). **Setting** Brooklyn, New York; Indianapolis, Indiana; Iowa City, Iowa; San Diego, California; Farmington, Connecticut; and St Louis, Missouri, USA. **Participants** A total of 606 probands (25.7% female, mean age 37.7) with baseline and follow-up data and 606 of their 1st-degree relatives who had life-ime AUDs (45.8% female, mean age 36.2 years). **Measurements** Persistent AUD, non-abstinent remission and abstinent remission were based on self-report interview data on most recent AUD symptoms and alcohol consumption. Dependent variable was relatives' AUD/remission status. Independent variable was probands' AUD/remission status. **Findings** A total of 34.6% of probands and 20.6% of relatives were abstinent and 11.1% of probands and 22.8% of relatives were in non-abstinent remission. AUD/remission status was correlated significantly in related ($r = 0.23$, $P = 0.0037$) but not in unrelated pairs. A significant interaction of probands' abstinent remission with a variable representing related (versus unrelated, $P = 0.003$) pairs suggested a familial association for abstinent remission. In related pairs, individuals with an abstinent proband were more likely to be abstinent themselves than were individuals whose proband had persistent AUD [relative risk ratio = 3.27, 95% confidence interval (CI) = 1.56–6.85, $P = 0.002$]; this association was not significant in unrelated pairs. **Conclusions** The likelihood of abstinent remission among people with alcohol use disorder appears to be more than three times greater for individuals who are related to an abstinent proband versus those related to a proband with persistent alcohol use disorder.

Keywords Alcohol dependence, alcohol use disorders, AUD, COGA, environmental, familial, genetic, remission, social.

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INTRODUCTION

The substantial body of evidence supporting familial influences on the development of alcohol use disorders (AUDs), both genetic and environmental [1–9], lacks a correspondingly large literature regarding familial influences on remission from AUDs. Studies that have included family history of AUD as a predictor of remission in AUD-affected individuals have yielded few significant results, regardless of how remission was defined. In a

national population-based investigation, family history of AUD was associated with non-abstinent remission cross-sectionally but not longitudinally, and had no association with abstinent remission [10,11]. In a male sample ascertained at birth and followed throughout 40 years, paternal AUD predicted higher risk for developing an AUD but had no association with the likelihood of abstinent or non-abstinent remission [12]. Family history of AUD was not associated with remission, defined as absence of AUD symptoms without regard to alcohol consumption, in population-based data [13] or in a Native American sample [14]. The lack of evidence for familial influences on remission from AUDs contrasts sharply with evidence that the heritability for the development of AUDs is 50–60% [4,5,9], and suggests that a phenotype derived from symptoms that characterize the development of an AUD may be insufficient to test familial influences on remission from that disorder.

Some factors influencing remission may overlap with those influencing the development of AUDs but others might be distinct, and may even diverge from the dimension of liability underlying AUDs [15]. Substance use disorders are often conceptualized as lying on an externalizing dimension which is characterized by impulsive and antisocial behavior [16] and which has substantial evidence for familial transmission [17–20]. Many questions used to tap behavioral symptoms of AUDs, such as whether alcohol was used in physically hazardous situations or social and interpersonal problems stemming from alcohol use, are at the same time addressing externalizing behaviors consistent with this conceptualization. Externalizing disorders are associated with poorer substance abuse treatment outcomes in clinical samples [21,22] but, among abstinent individuals with histories of alcohol dependence, externalizing traits do not necessarily inhibit the ability to remit [23–26]. For example, abstinent men and women recruited from a variety of sources (e.g. bars, community centers, Alcoholics Anonymous meetings) had more life-time antisocial personality disorder (ASPD) symptoms and scored higher on trait measures of antisocial disposition (e.g. MMPI-2 Psychopathic Deviance Scale) than did non-alcoholic controls, but did not differ from controls on six of seven current ASPD symptoms, suggesting that antisocial behaviors were reduced and abstinence maintained despite an underlying antisocial disposition [25]. Therefore, attempts to predict abstinent remission in a family member using life-time AUD in another family member, a phenotype based in large part on externalizing behaviors which might not be observed in abstinent individuals, may not provide an optimal test of familial influences on remission and may account for the null findings to date.

In contrast, some of the most consistent correlates of both abstinent and non-abstinent remission are social connections such as marriage, friendship and religious or self-help group attendance [27–30]. Traits that might enhance these connections, such as social cognition [31–33], might also be associated with the ability to remit. Heritable characteristics that are related to social cognition, such as prosocial behavior and social responsiveness [34,35], may represent a dimension that underlies remission in the same way that an externalizing dimension underlies AUDs, but that diverges from the externalizing domain. However, before heritable characteristics that might be associated with remission can be identified, a remission phenotype that displays a familial association, and therefore suggests some underlying genetic or familial environmental mechanisms, is needed.

To our knowledge, just one previous study on remission has defined remission in both the target subject and the family member. That study used a population-based twin sample to examine the genetic and environmental contributions to the likelihood of remission, defined as absence of symptoms regardless of drinking status. Familial influences accounted for 11% of the variance associated with remission in females (attributable to genetic influences shared with AUD) and 37% in males (attributable to environmental influences shared with the co-twin) which decreased the likelihood of remission [36]. In the current study we used data from a high-risk family study, the Collaborative Study on the Genetics of Alcoholism (COGA), which has a high prevalence of life-time AUD in the relatives of probands [19] and thus provides enough AUD-affected, and thus potentially remitted, proband-relative pairs to model persistent AUD, non-abstinent remission, and abstinent remission in both subjects. Greater AUD severity was associated with decreased likelihood of non-abstinent remission and increased likelihood of abstinent remission in population-based data and in previous work in COGA [10,30,37], consistent with other studies that found abstinent individuals had more severe AUD histories than non-abstinent individuals [27,38,39]. Because AUD severity might influence familial associations of remission in a way similar to its association with familial transmission of AUD [40], we categorized remission as abstinent and non-abstinent. Modeling abstinent and non-abstinent remission in all family members with life-time AUD allows for the possibility that abstinent and non-abstinent remitted individuals may have characteristics, such as social responsiveness, that contribute to their ability to remit but that are different from those linked to their development of AUDs. The goals of this study were to estimate the strength of the association of probands' persistent AUD, non-abstinent remission and abstinent remission (hereafter referred to as 'AUD/remission status') with relatives' AUD/remission status, and to test whether

this association differed in related and unrelated proband-relative pairs.

METHODS

Sample

Probands were recruited from consecutive admissions to in-patient, out-patient and aftercare alcohol or drug treatment settings within six catchment areas in the United States: Brooklyn, New York; Indianapolis, Indiana; Iowa City, Iowa; San Diego, California; Farmington, Connecticut; and St Louis, Missouri [41]. Probands were required to meet criteria for DSM-III-R alcohol dependence [42] and Feighner definite alcoholism [43], and to have at least two first-degree relatives available for study in the catchment area; all first-degree relatives were sought for baseline and follow-up interviews 5 years later [19,44]. The COGA protocol was approved by the institutional review board at each research site and all subjects provided written informed consent.

Of the probands who were interviewed at baseline (n = 1247), 793 (63.6%) were interviewed at the 5-year follow-up (Supporting information, Fig. S1 provides a flow-chart of proband selection). Of these, nine had incomplete data to inform AUD remission status, leaving 784 probands with baseline and follow-up interviews and AUD remission status. Of these, 178 were excluded from the current study because they did not have a first-degree relative with life-time AUD, necessary to the purpose of this study, leaving 606 probands for the current analysis. These probands comprised the index group with whom relatives were paired. Half of probands (n = 303) were selected randomly and paired with a biologically related first-degree relative; the remaining probands were paired with a randomly selected, unrelated individual of the same race from the remaining group of first-degree relatives. The pool of relatives available for matching to probands comprised 2305 first-degree relatives with life-time AUD who participated in the baseline or the 5-year follow-up interview.

The sample was divided approximately evenly among ascertainment sites, with 101 (16.7%) probands from Connecticut, 74 (12.2%) from Indiana, 88 (14.5%) from Iowa, 122 (20.1%) from New York, 81 (13.4%) from St Louis and 140 (23.1%) from California. Probands who were not interviewed at follow-up and thus excluded from this analysis, compared to probands who were interviewed at both time-points, met fewer life-time AUD criteria [mean ± standard deviation (SD) = 9.45 (1.89) versus 9.82 (1.57), $t_{(1245)} = -3.72$, $P < 0.001$] and conduct disorder criteria [mean ± SD = 2.01 (2.14) versus 2.36 (2.02), $t_{(1245)} = -2.92$, $P < 0.01$], on average, and had a lower prevalence of major depressive disorder (14.96% versus 22.95%, $\chi^2_{(1)} = 11.41$, $P < 0.001$). Probands who were excluded because they did not have a first-degree relative with AUD, compared to those with an affected relative, met fewer conduct disorder criteria [mean ± SD = 2.04 (1.84) versus 2.46 (2.08), $t_{(782)} = -2.44$, $P = 0.02$], and had a lower prevalence of females (20.79 versus 28.22%, $\chi^2_{(1)} = 3.90$, $P = 0.05$).

Assessment and definitions

All subjects were interviewed with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a comprehensive diagnostic instrument designed to accommodate several diagnostic systems, including DSM-III-R [42] and DSM-IV [45].The SSAGA includes detailed assessments of alcohol and drug use as well as substance-related and non-substance psychiatric disorders [46,47]. In this study, life-time DSM-5 AUD criteria [48] were based on three DSM-IV abuse symptoms (excluding legal problems), craving (which replaced the DSM-IV abuse criterion for legal problems in DSM-5) and seven DSM-IV dependence symptoms. DSM-5 AUD was operationalized as two or more of 11 possible criteria occurring in the same 12-month period, with recency noted as the last age any criterion (other than craving) was reported. Consistent with DSM-5, remission was defined as the absence of all 10 AUD criteria, other than craving, for at least 12 months. In these analyses, remission was characterized as non-abstinent or abstinent (no alcohol consumption for 12 months), based on the most recent information about AUD symptoms and alcohol consumption. The AUD/remission status for probands and for relatives who participated in the follow-up was based on their 5-year follow-up. For relatives with only one interview, AUD/remission status was based on recency of AUD symptoms at the time of interview.

Covariates

Additional variables were included in the multivariable regression analysis to adjust the association of probands' with relatives' AUD/remission status for important correlates of remission. These included demographics [age at most recent interview, female sex (versus male), self-reported ethnicity (African American versus European American and Other)], maximum life-time AUD criterion count (range = 2–11), conduct disorder criterion count (range = 0–15 conduct disorder criteria with occurrence before age 15), life-time history of major depressive disorder, history of professional treatment for alcohol problems and self-help group (e.g. Alcoholics Anonymous) attendance. A dummy variable coded 1 for related proband-relative pairs and 0 for unrelated pairs was also included.

Statistical analysis

Descriptive statistics for covariates were calculated by AUD/remission status. The bivariate association of each covariate with AUD/remission status was tested using multinomial regression analysis with persistent AUD as the reference category. Concordance rates for AUD/remission status in related and unrelated pairs were calculated. Relatives' AUD/remission status was the dependent variable in a multivariable multinomial logistic regression, with relatives' persistent AUD as the reference category and non-abstinent and abstinent remission as the two outcome categories. The primary independent variables were proband non-abstinent and abstinent remission; their association with relatives' remission status was adjusted for the covariates listed above. The interactions of proband non-abstinent and abstinent remission with the dummy variable representing related pairs were tested one at a time in the fully adjusted regression to determine whether the association of probands' AUD/remission status with relatives' AUD/remission status varied in related and unrelated pairs. The final regression was calculated separately in related and unrelated pairs. The Huber–White robust variance estimator was used to adjust for the clustering of family data. Data sets and variables were created using SAS statistical software, version 9.2 [49]. Analyses were performed using Stata Statistical Software, version 14.2 [50].

RESULTS

Abstinence was the most common type of remission in probands (34.6%), with lower rates of non-abstinent remission (11.1%). In relatives, rates of non-abstinent and abstinent remission were similar (22.8 and 20.6%, respectively). Among remitted individuals, abstinent and non-abstinent remission accounted for 75.8 and 24.2% of probands and 47.5 and 52.5% of relatives, respectively. Nearly half (49.6%) of abstinent relatives and 40.9% of non-abstinent relatives had been remitted for at least 10 years; an additional 23.1% of abstinent and 20.9% of non-abstinent relatives had been remitted for 5–9 years. Among probands who met AUD criteria at baseline, 75.2% of abstinent and 52.2% of non-abstinent individuals had been remitted for 5 years (since their baseline interview). Relatives were slightly but not significantly younger than probands when they entered the study [M(SD) = 36.2 (11.7) versus 37.7 (10.1), $P = 0.52$] and had a larger proportion of females (45.8 versus 25.7%, $\chi^2_{(1)=}5.4$, $P = 0.02$). Relatives had a lower mean number of life-time AUD symptoms than did probands, but this was not statistically significant. There were no significant differences between relatives and probands on other covariates, with the exception of professional treatment, which was not calculated due to 100% prevalence in probands. Among relatives who received professional treatment or attended self-help meetings, 52.8% had their first treatment or attended their first meeting before the proband's first treatment, 44.8% were treated after the proband's first treatment and 2.4% were treated during the same year.

Characteristics of relatives and probands by their respective AUD/remission statuses are displayed in Table 1.

Relatives

Abstinent and non-abstinent relatives were significantly older than relatives with persistent AUD (both $P < 0.01$). Non-abstinent remitters had a larger proportion of females than the persistent AUD group ($P = 0$ .03). Abstinent relatives had more life-time AUD symptoms and non-abstinent relatives had fewer than did relatives with persistent AUD (both $P < 0.001$). Compared to relatives with persistent AUD, abstainers had higher rates of professional treatment ($P = 0.03$) and self-help attendance ($P < 0.001$) and non-abstinent relatives had lower rates of professional treatment ($P < 0.01$). Both remitted groups had a higher life-time prevalence of major depressive disorder than the persistent AUD group (both $P < 0.01$).

Probands

Abstinent probands were slightly older ($P = 0.04$), had fewer African Americans ($P = 0.05$) and a greater number of life-time AUD symptoms than did probands with persistent AUD ($P = 0.03$). No other significant differences by AUD/remission status were observed (Table 1).

The distribution of AUD/remission status in related and unrelated pairs is shown in Table 2. The overall correlation for AUD/remission status was significant in related pairs ($r = 0.23$, $P = 0.0037$) but not in unrelated pairs. Related pairs had greater concordance than unrelated pairs for persistent AUD (61.8 and 52.6%, respectively) and abstinent remission (50.0 and 32.4%, respectively).

In the multinomial regression with relatives' AUD remission status as the outcome, adjusted for all covariates, the interaction between probands' abstinent remission and the variable representing related pairs (versus unrelated pairs) was significant [relative risk ratio (RRR) = 4.37, 95% confidence interval (CI) = 1.62–11.79, $P = 0.004$] and therefore the regressions were calculated separately in related and unrelated pairs (Table 3, full results available in Supporting information, Table S1). In related pairs, individuals with an abstinent proband were more than three times as likely to be abstinent themselves when compared to individuals related to a proband with persistent AUD (RRR = 3.27, 95% CI = 1.56–6.85, $P = 0.002$); this association was not significant in unrelated

Table 1 Characteristics of 606 first-degree relatives paired with probands and of the 606 probands ascertained from treatment settings with whom they were paired, by AUD remission status.

	Relatives			*Probands*		
		Remitted			*Remitted*	
	Persistent AUD[a] *(n = 343)*	*Non-abstinent (n = 138)*	*Abstinent (n = 125)*	*Persistent AUD*[a] *(n = 329)*	*Non-abstinent (n = 67)*	*Abstinent (n = 210)*
Age at study entry, mean (SD)	33.80 (10.74)	35.56 (10.57)*	42.58 (13.21)*	37.03 (10.07)	38.45 (9.26)	38.65 (10.48)
Age when AUD status calculated, mean (SD)	36.28 (10.96)	39.10 (10.74)*	45.74 (12.61)*	42.67 (10.06)	44.10 (9.16)	44.53 (10.48)*
Female, %	43.15	54.35*	44.00	26.44	20.90	26.19
African American, %	20.12	18.84	15.20	20.97	22.39	13.81*
AUD symptoms, life-time, mean (SD)	6.19 (2.80)	5.05 (2.66)*	7.98 (2.81)*	9.83 (1.54)	9.69 (1.61)	10.11 (1.31)*
Alcohol treatment						
Professional	30.61	18.12*	41.60*	100.00	100.00	100.00
Self-help	33.24	24.64*	63.20*	97.87	95.52	98.57
Conduct disorder symptom count	1.97 (1.77)	1.63 (1.79)	2.06 (2.14)	2.36 (2.04)	2.46 (2.37)	2.44 (2.05)
Major depressive disorder, life-time	20.41	31.88*	36.00*	24.92	29.85	20.48

[a]Persistent alcohol use disorder (AUD) is reference category for all tests; *$P < 0.05$ in relation to the persistent AUD group. SD = standard deviation.

Table 2 Distribution and concordance for AUD/remission status in related and unrelated pairs.

	Relatives' status			
Related pairs	AUD	Non-abstinent remission	Abstinent remission	Total
Proband status				
AUD	105 (61.8%)	44	21	170
Non-abstinent remission	17	9 (11.4%)	6	32
Abstinent remission	48	26	27 (50.0%)	101
Total	170	79	54	303
Unrelated pairs	AUD	Non-abstinent remission	Abstinent remission	Total
Proband status				
AUD	91 (52.6%)	30	38	159
Non-abstinent remission	17	8 (13.5%)	10	35
Abstinent remission	65	21	23 (32.4%)	109
Total	173	59	71	303

AUD = alcohol use disorders.

pairs. No other significant associations of probands' with relatives' AUD remission status were observed.

DISCUSSION

This study explicitly modeled abstinent and non-abstinent remission in probands who were recruited from AUD treatment programs and in their first-degree family members with life-time AUDs to test for familial associations of remission in high-risk families and to define a phenotype which can be used to explore associations of remission with potentially heritable characteristics. Results showed that individuals who were related to an abstinent proband were more than three times as likely to be abstinent themselves, compared to individuals related to a proband with persistent AUD; this association was not significant in unrelated pairs. The significant association of probands' with relatives' abstinent remission in related but not in unrelated proband-relative pairs suggests there are familial influences on abstinent remission which may be due to genetic or familial environmental factors. The familial association of abstinent remission in this sample selected for high-risk for AUDs has not been observed previously.

The association of abstinence in one family member with abstinence in another stands in contrast to a host of null findings regarding familial influences on remission

Table 3 Results of multinomial regression showing associations of probands' AUD remission status with relatives' AUD remission status in related and unrelated pairs, adjusted for covariates.

	Relatives' AUD remission status (outcome)		
		Remitted	
	Persistent AUD RRR (95% CI)	*Non-abstinent versus persistent AUD RRR (95% CI)*	*Abstinent versus persistent AUD RRR (95% CI)*
Related pairs (n = 303)			
Proband AUD	1.00	1.00	1.00
Proband non-abstinent remission	1.00	1.23 (0.45–3.33)	2.50 (0.80–7.82)
Proband abstinent remission	1.00	1.42 (0.75–2.68)	**3.27 (1.56–6.85)**
Unrelated pairs (n = 303)			
Proband AUD	1.00	1.00	1.00
Proband non-abstinent remission	1.00	1.77 (0.64–4.92)	1.68 (0.61–4.61)
Proband abstinent remission	1.00	1.10 (0.55–2.19)	0.78 (0.38–1.61)

RRR = relative risk ratio, 95% CI = 95% confidence interval; significant results shown in bold type; adjusted for DSM-5 alcohol use disorders (AUD) criterion count, life-time professional treatment, life-time self-help attendance, major depressive disorder, conduct disorder criterion count, sex, age at most recent interview, ethnicity. Reference category for each remission category is persistent AUD.

from other studies in population-based [11,13], high-risk and clinical samples [12,14,51,52] using a variety of definitions of remission. The current analyses used an explicit abstinent and non-abstinent remission phenotype, distinct from AUDs and consistent with the idea that the distribution of risks for development of, and for remission from, AUDs may not lie on the same continuum [15]. Our results suggest that there may be genetic or familial environmental influences on abstinent remission and demonstrate that departing from the more common risk-factor-to-remission comparisons within families may indeed prove useful. When remission is the target phenotype, remission in all family members should be measured explicitly, rather than measuring it as an outcome only in target subjects but not in their relatives. This will facilitate the examination of potentially heritable characteristics underpinning abstinent outcomes, such as social responsiveness, that may increase the likelihood of remission, as well as the investigation of family environments associated with remission from AUDs. Much more work will need to be conducted to identify heritable traits that may be related to abstinent remission and to probe for mediators and moderators of their effect.

In addition to potentially heritable effects on abstinent remission, another explanation for the current findings might rest with a social contagion model, or the spread of behavior within a family due to social proximity. Analysis of large social networks from a population-based study indicated that both heavy drinking and abstinence clustered in networks, and also that the heavy drinking or abstinence of relatives and friends at one time-point were associated with changes in the subject's alcohol consumption, to heavier drinking or abstinence, at a subsequent time-point [53]. The same may be true within families affected by severe AUDs, where abstinence in one person may influence another family member with an AUD to try to quit drinking. This possibility is consistent with evidence that abstinence is the most stable form of remission among individuals with severe AUDs [11,54–56]. If older family members with life-time AUD are abstinent as younger family members are developing alcohol problems, it is possible that younger members, if they recognize severe problems in themselves, may look to older members for direction or example, or that older members may recognize problems in younger members and intervene. In fact, analysis of twin data showed that the variance associated with treatment-seeking for alcohol problems was accounted for primarily by familial influences, with 41% of the variance due to genetics, 40% due to shared environment, and just 19% to unique environment [57]. In the current study, all probands had by definition been treated, which precluded examination of familial associations for treatment-seeking; however, abstinent relatives had the highest rates of treatment-seeking in the sample, suggesting an association of relatives' with probands' treatment-seeking.

More than 40% of probands and relatives were remitted in this high-risk sample, with abstinence the most common type of remission in probands and abstinent and non-abstinent remission equally common in relatives. An earlier study in the COGA sample found that more than 50% of all subjects with life-time alcohol dependence (probands, relatives and controls) reported periods of abstinence lasting 3 months or more, with 16.1% reporting abstinence of 5 or more years [37]. Similar to the relatives in the current study, abstainers were older

than individuals who never abstained, had a greater number of life-time symptoms and were more likely to have sought formal treatment and to have attended self-help groups. Other sampling frames also show similarities to the current data. Abstinent individuals with life-time AUD from population-based data had more AUD symptoms than remitted non-abstinent individuals [27]. In a national sample of individuals self-identified as 'in recovery', abstainers compared to non-abstainers were older, more likely to have received professional treatment and to have attended self-help meetings, and had significantly more life-time alcohol dependence symptoms [38]. These similarities across a range of samples suggest that individuals who become abstinent, regardless of sampling frame, represent a severe end of the AUD continuum. In the current study, abstinence may represent a common end-point for individuals with severe AUD. It is possible that non-abstinent remitters will become abstinent for a period, or periods, of time. Given that nearly half (49.6%) of abstinent relatives in the current study had been remitted for 10 or more years, abstinence may indeed represent an end-point for subjects who remit from severe AUDs.

Limitations

All phenotypes were based on self-report without confirmation from collateral reports. The remission phenotypes in the current study did not account for past relapses or the possibility of future relapses. Remission was based on at least 12 months without symptoms, and thus might be a premature classification given that risk of relapse is reduced after 5 years of remission and continues to decline thereafter [54]. The prevalence of non-abstinent remission in probands was low and the absence of significant findings concerning non-abstinent remission in this study does not preclude the possibility that it may have a familial association in a sample with more non-abstinent remitters. The sample was selected for high familial risk for alcoholism, and therefore results are not necessarily generalizable to AUD samples drawn from population-based data, although our sample may be informative for clinical populations.

Conclusions

The likelihood of abstinent remission was more than three times greater for individuals who were related to an abstinent proband versus those related to a proband with persistent AUD. Identifying characteristics that underpin this familiality, and whether it is entirely environmental, heritable or a combination, is a challenge for future study.

Declaration of interests

None.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 Results of multinomial regression showing associations of proband alcohol use disorder (AUD) remission status with relatives' AUD remission status, with covariates.

Figure S1 Flow-chart of proband selection for study of remission.